Remarks

Claims 1-17 were previously pending in the subject application. By this Amendment, claims 2, 4 6 and 12 have been amended, claims 1, 3, 5, 7 and 13 have been cancelled, and new claims 18-21 have been added. Support for the claim amendments and new claims can be found throughout the subject specification. No new matter has been added by these amendments and new claims. Accordingly, claims 2, 4, 6, 8-12 and 14-21 are currently before the Examiner for consideration.

Initially, the applicants wish to acknowledge and express their appreciation for the Examiner's indication of allowable subject matter. The amendments to the claims have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution by focusing the claims on allowable subject matter. These amendments should not be taken to indicate the applicant's agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 1-17 have been objected to because of informalities. The applicants appreciate the Examiner's careful review of the claims, and the applicants have amended their claims herein to adopt the language suggested by the Examiner. The applicants respectfully request reconsideration of the claim objections in view of the amendments set forth herein.

Claims 1 and 2 have been rejected under 35 U.S.C. §102(b) as being anticipated by Slieker *et al.* The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination. Specifically, the Slieker *et al.* reference does not disclose or suggest the specific advantageous insulin analogues now claimed by the current applicants.

Of course, it is well established that to anticipate, a single prior art reference must disclose all of the elements of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims,

> determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra*; *Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

In *Dewey & Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

Please note that the anticipation rejection based on the Slieker *et al.* reference has been rendered moot with respect to claim 1 in view of the cancellation herein of claim 1. The applicants have presented herein new claim 18 which, for purposes of clarity and to expedite prosecution, focuses on analogues that have an Ala substituted for Tyr at the 16th or 26th position of the B-chain of human insulin and a deletion of Phe at the B1 position. As noted in the outstanding Office Action, Slieker *et al.* do not teach analogues having the B1 deletion. Thus, Slieker *et al.* do not teach each and every limitation in the applicants' claims. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on Slieker *et al.*

Claims 1, 2, 6, 8, 12 and 14 have been rejected under 35 U.S.C. §102(b) as being anticipated by Chance *et al.* (WO 9414461). The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination. As discussed below, Chance *et al.* do not disclose the specific insulin analogues now claimed. Nor does the Chance *et al.* reference disclose the pharmaceutical compositions or methods of treatment as now set forth in the applicants' claims.

With regard to the claims to the analogues themselves, please note that claim 1 has now been cancelled and that claim 18 specifies a substitution of Ala for Tyr at the 16th or 26th position of the human insulin B-chain and a deletion at the B1 position. Chance *et al.* do not teach insulin analogues having these characteristics.

With regard to the method of treatment claims, the Chance *et al.* reference does not disclose a method for treating an insulin deficiency by administering an insulin analogue wherein the Tyr at the 16th or 26th position of the B chain of human insulin is substituted by Ala, and wherein the analogue has a deletion at either one or both of Phe at position 1, B1, or Thr at position 30, B30, of the B-chain of human insulin. Nor do Chance *et al.* disclose a method for treating an individual having an insulin deficiency by administering an insulin analogue having the Tyr at the 16th position of the human insulin B-chain substituted by Ala, and wherein there is no deletion of B1 Phe or the B30 Thr.

Consistent with the absence of any teaching in the Chance *et al.* reference of the applicants' claimed methods, there is also no teaching of the pharmaceutical compositions as now claimed by the current applicants. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on Chance *et al.*

Claims 1, 2 and 4 have been rejected under 35 U.S.C. §102(b) as being anticipated by Kristensen *et al.* The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination. Specifically, Kristensen *et al.* do not disclose or suggest the specific advantageous insulin analogues claimed by the current applicants.

Please note that the anticipation rejection based on the Kristensen *et al.* reference has been rendered moot with respect to claim 1 in view of the cancellation herein of claim 1. The applicants have presented herein new claim 18 which, for purposes of clarity and to expedite prosecution, focuses on analogues that have an Ala substituted for Tyr at the 16th or 26th position of the B-chain of human insulin and a deletion of Phe at the B1 position. As noted in the outstanding Office Action, Kristensen *et al.* do not teach analogues having the B1 deletion. Thus, Kristensen *et al.* do not teach each and every limitation in the applicants' claims. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on Kristensen *et al.*

Claims 6, 8, 10, 12, 14, and 16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kristensen *et al.* as applied to claims 1, 2 and 4 above, and further in view of Chance *et al.* The applicants respectfully traverse this ground for rejection because the cited references, alone, or in combination, do not disclose or suggest the applicants' claimed methods and pharmaceutical compositions.

The applicants appreciate the Examiner's indication that certain claims are allowable. Specifically, the outstanding Office Action states that "the prior art does not teach nor suggest the combination of modification of the in position B16 or B26 and the deletion of B30 or B1 in the b-chain of the insulin." In addition to the allowability of claims reciting analogues with both the modification and the deletion, the applicants respectfully submit that claims to the use of analogues with the B16 modification, even without a deletion, are novel and non-obvious.

The applicants respectfully submit that the identification of advantageous insulin analogues has been largely empirical. Thus, any results that might be achieved in the context of Chance *et al.* are independent of the teachings of Kristensen *et al.*, and vice versa. The skilled artisan could not conclude from certain Kristensen *et al.* assays, even in view of Chance *et al.*, that therapeutic utility could be expected of a certain analogue, independent of the nature of the substitution.

Therefore, from the cited references, at most, it may be obvious to try various analogues. However, the "obvious to try" standard has long been held to be an inappropriate basis for a §103 rejection. See, for example, *In re* Antonie, 195 USPQ 6 (CCPA 1977); *In re Dow Chemical Co.*, 5 USPQ2d 1529 (CAFC 1988). Rather, a finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, neither reference contains a suggestion of the advantageous properties of the specified insulin analogues for treating insulin deficiency. It is only the applicants' disclosure that provides such a teaching, and the applicants' disclosure cannot be used to reconstruct the prior art for a rejection under §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The mere fact that the purported prior art could have been modified or applied in a manner to yield applicants' invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art . . . ." *In re Dow Chemical Co., supra* at 1531. In the references cited in support of the §103 rejection, one finds neither.

Please note that Kristensen *et al.* specifically state (page 12982, second column, second full paragraph) that the B16 and B26 mutations "only altered affinity for the insulin receptor moderately ...indicating that these residues are not part of the functional binding epitope." Accordingly, Kristensen *et al.* would lead the skilled artisan away from the use of such insulin analogues in therapy. It must be emphasized that the subject invention was made only as a fortuitous result of extensive research. It is only after reading the applicants' own disclosure that a person skilled in this art would have knowledge to use these particular anlogues. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103 based on Kristensen *et al.* and Chance *et al.*

In view of the foregoing remarks, and the amendments to the claims and the submission of new claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§§1.16, 1.17, or 1.492 as required by this paper to Deposit Account No. 19-0065.

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The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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